REMARKS

1. STATUS OF THE CLAIMS

Claims 1-17 were originally filed in the present application. Claims 1-17 are currently pending in the present application.

2. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner asserts that claims 1 and 17 are indefinite because the term "from about" is not defined. The present rejection is moot in view of the amendments to the claims deleting the term "from about" from each claim.

The Examiner asserts that claim 1 is indefinite because step (c) allegedly fails to relate to the preamble. In this regard the Examiner asserts that the engrafted cells would need to recapitulate the leukemia. The Examiner is respectfully directed to page 5, lines 25-27 of the specification wherein it is disclosed that the term "engrafted" means that the leukemia cells have migrated throughout the rodent, thus establishing the human model of leukemia in the rodent.

The Examiner asserts that claim 4 is vague and indefinite because it recites the term "about". The present rejection is moot in view of the amendment to claim 4. Support for the amendment to claim 4 is found in the specification at page 3, line 1.

The Examiner asserts that claim 5 is vague and indefinite because it recites the term "about". The present rejection is moot in view of the amendment to claim 5 which deletes the term "about".

The Examiner asserts that claim 7 is vague and indefinite because it recites the term "about". The present rejection is moot in view of the amendment to claim 7.

The Examiner asserts that claim 12 is unclear because it would be expected that the claimed rodent would have more than one leukemia-initiating cell. The present rejection is moot in view of the amendment to claim 12.

The Examiner asserts that claim 17 is unclear because step (c) allegedly fails to relate to the preamble. In this regard the Examiner asserts that the engrafted cells would need to recapitulate the leukemia. The Examiner is respectfully directed to page 5, lines 25-27 of the specification wherein it is disclosed that the term "engrafted" means that the leukemia cells have migrated throughout the rodent, thus establishing the human model of leukemia in the rodent.

3. CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

A. REJECTION OVER BLAIR ET AL.

The Examiner rejected claims 10-16 under 35 U.S.C. § 102(b) as allegedly being anticipated by Blair et al. (1997) Blood 89:3104-3112. The present rejection is respectfully traversed.

Claim 10 is directed to an *in vivo* model of human leukemia produced by a process that includes a step of injecting the rodent with an effective pre-conditioning amount of mononuclear cells derived from human fetal cord blood and a step of maintaining the rodent for 5 to 10 days. Blair does not disclose either of these steps used in the production of a mouse having leukemia cells. Thus, Blair does not disclose a rodent model of human leukemia wherein the rodent model has a complement of normal human cells. Therefore, Blair cannot anticipate claim 10.

Claims 11 is directed to an immunodeficient rodent having human fetal cord blood cells and having engrafted human leukemia cells. Blair does not disclose an immunodeficient rodent having engrafted human leukemia cells, wherein the rodent also has human fetal cord blood cells. Therefore, Blair cannot anticipate claim 11. Claims 12-16 depend from claim 11 and, therefore, Blair cannot anticipate claims 12-16 because independent claim 11 is not anticipated by Blair.

B. REJECTION OVER STEELE ET AL.

The Examiner rejected claims 10-16 under 35 U.S.C. § 102(b) as allegedly being anticipated by Steel et al. (1997) Blood 90:2015-2019. The present rejection is respectfully traversed.

Claim 10 is directed to an *in vivo* model of human leukemia produced by a process that includes a step of injecting the rodent with an effective pre-conditioning amount of mononuclear cells derived from human fetal cord blood and a step of maintaining the rodent for 5 to 10 days. Steele does not disclose either of these steps used in the production of a mouse having leukemia cells. Thus, Steele does not disclose a rodent model of human leukemia wherein the rodent model has a complement of normal human cells. Therefore, Steele cannot anticipate claim 10.

Claims 11, as amended, is directed to an immunodeficient rodent having human fetal cord blood cells and having engrafted human leukemia cells. Steele does not disclose an immunodeficient rodent having engrafted human leukemia cells, wherein the rodent also has human fetal cord blood cells. Therefore, Steele cannot anticipate claim 11. Claims 12-16 depend from claim 11 and, therefore, Steele cannot anticipate claims 12-16 because independent claim 11 is not anticipated by Steele.

4. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

A. REJECTION OVER BLAIR ET AL. IN VIEW OF HAYNESWORTH AND CAPLAN

The Examiner rejected claims 1-5, 7-9, and 17 under 35 U.S.C. § 103(a) over Blair et al. (1997) Blood 89:3104-3112 in view of U.S. Patent No. 5,733,542 to Haynesworth et al. and in view of U.S. Patent No. 5,486,359 to Caplan et al. The present rejection is respectfully traversed.

The present claims are directed to a process for making an *in vivo* model of human leukemia comprising: pre-conditioning an immunodeficient rodent with a sub-lethal dose of irradiation and injecting the rodent with a pre-conditioning amount of mononuclear cells derived from human fetal cord blood (bone marrow in claim 17); maintaining the rodent for 5 to 10 days; and injecting the rodent with an effective engrafting amount of primary human leukemia cells.

The Examiner asserts that, Blair teach the injection of human acute myeloid leukemia (AML) cells in NOD/scid mice, that Haynesworth teach a method for enhancing bone marrow engraftment by administration of mesenchymal stem cells, and that Caplan teach the isolation and purification of human mesenchymal stem cells. Next, the Examiner alleges that "it would have been obvious for one of ordinary skill in the art to modify the mouse model, as taught by Blair, by pre-conditioning the mouse with mesenchymal stem cells obtained from human fetal cord blood, as taught by Haynesworth and Caplan, with a reasonable expectation of success".

To the contrary, the cited art being combined in the rejection do not provide a suggestion or motivation to modify a reference or to combine the references with a reasonable

expectation of success as alleged by the Examiner.

Blair does not provide a suggestion or motivation to pre-condition a rodent with mononuclear cells or to establish the mononuclear cells *in vivo* in the rodent prior to engrafting primary human leukemia cells. Caplan does not provide a suggestion or motivation to pre-condition the rodent or to engraft primary human leukemia cells. Haynesworth does not provide a suggestion or motivation to use a pre-conditioning step carried out *in vivo* in the rodent or a preconditioning step prior to injecting primary human leukemia cells. There was no expectation of success in Blair, Haynesworth, or Caplan that prior administration of mononuclear cell or bone marrow cells would enhance engraftment of primary human leukemia cells in an *in vivo* model.

The present invention discloses that pre-conditioning rodents with mononuclear cells derived from human fetal cord blood prior to engrafting primary human leukemia cells, results in a surprising three to ten fold enhancement in the percent level of leukemia engraftment (see Figure 4A). Blair, Haynesworth, and Caplan do not disclose this surprising three to ten fold enhancement in the percent level of leukemia engraftment.

Accordingly, the present claims are not obvious over Blair in view of Haynesworth and Caplan because the cited references do not disclose a suggestion to modify the teachings of the cited references to arrive at the claimed invention with a reasonable expectation of success, the cited references do not teach all limitations of the claims, and because the cited references do not disclose the surprising three to ten fold enhancement in engraftment of primary human leukemia cells observed in the

present invention.

B. REJECTION OVER STEELE ET AL. IN VIEW OF HAYNESWORTH AND CAPLAN

The Examiner rejected claims 1, 2, 4-9, and 17 under 35 U.S.C. § 103(a) over Steele et al. (1995) Blood 86:782A in view of U.S. Patent No. 5,733,542 to Haynesworth et al. and in view of U.S. Patent No. 5,486,359 to Caplan et al. The present rejection is respectfully traversed.

The Examiner asserts that, Steele teach the injection of human T-cell acute lymphoblastic leukemia (T-ALL) cells in SCID mice, that Haynesworth teach a method for enhancing bone marrow engraftment by administration of mesenchymal stem cells, and that Caplan teach the isolation and purification of human mesenchymal stem cells.

The Examiner alleges that, "it would have been obvious for one of ordinary skill in the art to modify the mouse model, as taught by Steele, by pre-conditioning the mouse with mesenchymal stem cells obtained from human fetal cord blood, as taught by Haynesworth and Caplan, with a reasonable expectation of success".

To the contrary, the cited art being combined in the rejection do not provide a suggestion or motivation to modify a reference or to combine the references with a reasonable expectation of success as alleged by the Examiner. Steele does not teach pre-conditioning the rodent model with human cells prior to injecting T-ALL cells. The Examiner states that "Haynesworth differs from the claimed invention in that they do not teach MSCs isolated from human fetal cord blood". Of note, Haynesworth also does not teach enhancing the engraftment of

human primary leukemia cells.

There was no motivation suggested in Steele, Haynesworth, or Caplan to combine elements of the cited references to arrive at the present invention. There was no expectation of success in Steele, Haynesworth, or Caplan that prior administration of mesenchymal stem cells would enhance engraftment of primary human leukemia cells in an *in vivo* model.

The present invention discloses that pre-conditioning rodents with mononuclear cells derived from human fetal cord cells (or bone marrow) prior to engrafting primary human leukemia cells results in a surprising three to ten fold enhancement in the percent level of leukemia engraftment (see Figure 4A). Steele, Haynesworth, and Caplan do not disclose this surprising three to ten fold enhancement in the percent level of leukemia engraftment that results from the claimed pre-conditioning step.

Accordingly, the present claims are not obvious over Steele in view of Haynesworth and Caplan because the cited references do not disclose a suggestion to modify the teachings of the cited references to arrive at the claimed invention with a reasonable expectation of success, the cited references do not teach all of the claimed limitations, and because the cited references do not disclose the surprising three to ten fold enhancement in engraftment of primary human leukemia cells observed in the present invention.

CONCLUSION

Applicant respectfully submits that all pending claims are in condition for allowance and requests that the Examiner allow all pending claims. The Examiner is requested to contact the

representative for the Applicants, to discuss any questions or for clarification. No new matter is added by way of the present Response. If there are any further fees associated with this response, the Director is authorized to charge our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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